The Present Status of Immunization Against Diphtheria

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It is a pleasure to acknowledge the courtesy of the invitation to address the Academy and an honour to pay tribute to two of your illustrious members who have played such a prominent part in the control of diphtheria, namely William Halleck Park, and Béla Schick who is in the audience tonight. Time does not permit more than a very respectful nod to the past. It is to Ramon of the Pasteur Institute we owe the introduction of formol toxoid, a safe, easily standardized, inexpensive and very effective antigen for active immunization against diphtheria. The study of the effectiveness of toxoid in Toronto school children made at a time of high prevalence of diphtheria showed that three doses given at three weeks' interval resulted in a 90 per cent reduction as compared with the rate of their uninoculated school mates. That study initiated in 1927 had to be abandoned for the sole reason that the morbidity rate from diphtheria dropped to such a low figure and there maintained up to the present, as to make any comparison between the inoculated and non-inoculated meaningless.

Diphtheria has not been controlled by isolation and quarantine. Essentially, the control rests upon the simple principle of producing the most effective degree of active immunity in the greatest number of persons as early in life as possible and maintaining that immunity indefinitely. Administratively this looks like, and perhaps is, a formidable task. It has long been known that the response to toxoid and the loss of antitoxin are both subject to very wide individual variation. Both of these factors may be countered by giving the "dose de rappel" of Ramon, or more commonly designated recall or booster dose, in suitable quantity and at appropriate intervals. The basic principle of the secondary stimulus or recall dose has long been known. In 1898 Dean at Oxford showed the prompt and high rise in antitoxin in response to a secondary stimulus in a horse previously hyperimmunized and rested some years. Rufus Cole clearly enunciated that principle in 1904. He showed that a secondary stimulus in itself too small to elicit a detectable antibody response caused a rapid rise in agglutinins in an animal previously immunized and whose antibody titre had fallen to zero. More important perhaps than any other single factor in the control of diphtheria is the intelligent use of the recall dose.

There is a close analogy between active immunization against the diseases tetanus and diphtheria. Their respective toxoids readily call forth an antitoxic immunity which may be maintained at a high level when recall doses are given. This is perhaps best illustrated by the experience in the armed forces in regard to tetanus which was virtually eliminated in the recent war, one of the brilliant achievements of preventive medicine. The essence of this success lay in the fact that a recall dose of toxoid was accepted as a routine procedure. The unpublished results of tetanus antitoxin titrations of blood samples of some 2000 members of the armed forces indicate that all who had received the routine inoculations of toxoid, including the annual recall dose, showed a protective level of antitoxin ($>1/100$ u/cc). In contrast, in a small group of 53 who had not had a recall dose, only 62 per cent showed antitoxin at or beyond this level.

The effectivenes of minute doses of diphtheria antigen when given as a secondary stimulus is illustrated by the fact that a Schick test with control of diluted toxoid will produce a conversion from Schick positive to Schick negative in approximately 70 per cent of persons. The combined value

of the test toxin plus control is only 0.021 Lf. A secondary stimulus of Schick test toxin alone which represents only 0.001 Lf may give on the average a tenfold increase in antitoxin. To a group of twelve persons, all of whom possessed antitoxin initially, a secondary stimulus of 4 Lf of toxoid was given and blood samples taken daily for one week and at longer intervals thereafter up to six years. The first detectable increase in antitoxin was manifested by the fourth day; by the seventh day all had responded and the maximum titre was attained by the majority by the eleventh day. The highest level recorded in this small group was 120 units per cc. of serum. In a group of 340 persons, 95 per cent showed a response to toxoid when given as a secondary stimulus. These and similar studies were undertaken to determine the minimum, and at the same time practical, recall dose and to follow the level of antitoxin over a period of years. In general, the response in antitoxin varied with, though not in direct proportion to, the strength of the stimulus. In pre-school children where sensitivity to toxoid is not a problem, a recall dose of 20 to 40 Lf is desirable. In school populations, in order to avoid the necessity of a preliminary sensitivity test, 3 or 4 Lf of toxoid, because of its freedom from untoward effects and the satisfactory degree of antitoxin response, may be recommended as a recall dose. A similar dose is effective in adults, but except in the face of an epidemic, screening by a reaction test for sensitivity is desirable.

The rate of loss of antitovin as already mentioned is subject to wide individual variation. On the average, in a non-diphtheria environment, there is a loss in antitoxin of 60 per cent within two years as shown in a group of children studied in 1937. That is to say, taking the average antitoxin level of a group of immunized children as 0.33 u/cc, the average unitage has dropped to 0.13 u/cc in two years. Other studies have shown that from 10 to 30 per cent of persons revert to Schick positive within three to five years. It is quite apparent then that no success in the control of diphtheria may be expected without the recall dose.

The quality of toxoid is adequately safeguarded by the National Institute of Health. One may thus generalize by saying that any diphtheria toxoid given in two or three doses with an interval of three to six weeks may be expected to act as an effective primary stimulus. A recall dose given six to twelve months later will result in a protective level of antitoxin in well over 90 per cent. Without at least one recall dose the immunization procedure must be regarded as incomplete. In children immunized in infancy a second recall dose is recommended between the ages of eighteen and twenty-four months and a third when the child enters school. Possibly the second may be omitted, but because of the increased hazard of school a dose should be given at this time. In older children a booster dose is recommended every four or five years. In the armed forces approximately 50 per cent were Schick positive. In the recent epidemic at Halifax 45 per cent of cases were over fifteen years of age. Before diphtheria is effectively controlled adults will be required to be immunized. The administrative difficulties as well as the problems of reactions to toxoid are obvious. A preliminary screening with a Schick test and control of diluted toxoid (0.2 Lf/cc) which serves also as a "reaction test" is essential. Following this scheme, some hundreds of thousand personnel of the Royal Canadian Air Force were inoculated against diphtheria.

The use of multiple antigens will in some measure reduce the administrative burden of immunization. In a small series of very young children the response to diphtheria and tetanus toxoids was particularly striking after four doses of these antigens with pertussis vaccine added. There is good laboratory evidence to show that the bacterial element acts as an adjuvant.

With 600,000 cases of diphtheria per year reported in Europe there is no basis for complacency. Nothing less than a vigorous campaign of active immunization with a schedule of inoculations possibly more rigorous than necessary, is required to offset the menace of diphtheria in America.